Antimicrobial Stewardship News
Volume 8, Number 2
February 2020

Rapid Diagnostic Testing for Bloodstream Infections

Introduction

Studies consistently demonstrate that early appropriate antibiotic therapy for severe sepsis saves lives and that hourly delays in effective antibiotic treatment result in significant incremental increases in mortality.[1] This results in frequent use of empiric broad-spectrum antimicrobial therapy in effort to cover a wide range of potential pathogens. Unfortunately, conventional microbiology techniques often require 48-72 hours of incubation before providing organism identification and antimicrobial susceptibilities. MALDI-TOF, monoplex and multiplex PCR are all technologies designed to improve diagnostic turnaround. This newsletter reviews several rapid diagnostic technologies (RDT) available for bloodstream infections (BSI) and their applications to clinical outcomes.

Commercially Available BSI Rapid Diagnostics

A variety of rapid diagnostic technologies for bloodstream infection are currently available, each with nuanced distinctions.

Matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF) allows for identification of pathogens at the genus and species level by leveraging chemical signatures of organisms and comparing them to proprietary databases. However, MALDI-TOF technology does not permit any antimicrobial susceptibility testing (AST), and therefore cannot distinguish MRSA from MSSA, VRE from vancomycin-susceptible *Enterococcus*, etc. Identification usually requires 30-60 minutes from time of positive blood culture detection and Gram-staining.

Cepheid Xpert MRSA/MSSA utilizes PCR technology on blood cultures with Gram-positive staining to detect the presence of *spA* (indicating presence of *Staphylococcus aureus*) and *SCCmec*/*mecA* to distinguish MRSA from MSSA. Turnaround time for this test is approximately one hour, compared to roughly 24 hours for chromogenic culture methods.

BioFire FilmArray BCID, Verigene BC-GP, Verigene BC-GN, GenMark ePlex BCID and iCubate IC-System all employ multiplex PCR to identify a varying number of pathogenic organisms. These tests also permit the detection of several antimicrobial resistance genes, including *mecA*, *mecC*, *vanA*, *vanB*, and several genes signifying ESBL (*CTX-M*, *OXA*, etc.) and KPC organisms (*KPC, NDM*, etc.). However, they too are incapable of providing traditional AST with MIC values. Results return within 1-4 hours of blood culture positivity, depending upon the platform.

Nuclear magnetic resonance detection can rapidly detect pathogen DNA from whole blood testing without the need for positive blood cultures. T2 Biosystems currently markets the T2Candida and T2Bacteria tests which provide results for 5 *Candida* species and 6 bacteria (*E. faecium*, *S. aureus*, *K. pneumoniae*, *A. baumannii*, *P. aeruginosa*, and *E. coli*). These tests provide results within 4 hours of specimen processing.

Lastly, Accelerate Diagnostics utilizes fluorescent *in situ* hybridization to identify six Gram-positive pathogens and eight Gram-negative pathogens. Simultaneously, it utilizes time-lapse photography to provide phenotypic susceptibility testing within 7-8 hours of blood culture positivity, dramatically shortening the window to certain antibiotic susceptibility results. However, the results are still restricted to a limited number of antimicrobials.

Clinical Applications of RDT

Gram-positive Bacteremia

An estimated 119,247 episodes of *S. aureus* bacteremia occurred in 2017 in the United States, resulting in 19,832 associated deaths. Moreover, rates of community-acquired MRSA BSI have stagnated and rates of MSSA BSI

	BioFire® FilmArray® BCID	BioFire® FilmArray® BCID2	Verigene® BC-GP	Verigene® BC-GN	GenMark ePlex® BC-GP	GenMark ePlex® BC-GN	GenMark ePlex® BC-FP	Accelerate PhenoTest™ BC Kit	T2 Candida® Panel	T2 Bacteria® Panel	iCubate iC-GPC Assay™	iCubate iC-GN Assay™
Targets	27	43	16	15	26	29	15	14*	5	6	8	11
Resistance Detection	Yes (G)	Yes (G)	Yes (G)	Yes (G)	Yes (G)	Yes (G)	No	Yes (P)	No	No	Yes (G)	Yes (G)
Time to Result	~ 1 hr	~ 1 hr	~ 2.5 hrs	~ 2 hrs	~1.5 hrs	~1.5 hrs	~ 1.5 hrs	~ 7 hrs	~ 4 hrs	~ 4 hrs	~ 4 hrs	~ 4 hrs
Sample Required	Positive Blood Cx	Positive Blood Cx	Positive Blood Cx	Positive Blood Cx	Positive Blood Cx	Positive Blood Cx	Positive Blood Cx	Positive Blood Cx	Whole Blood	Whole Blood	Positive Blood Cx	Positive Blood Cx

Comparison of commercially available multiplex rapid diagnostic tests for bloodstream infections. Abbreviations: BC (blood culture), FP (fungal pathogens) GP (Gram-positive), GN (Gram-negative), G (genotypic), P (phenotypic). N/A (not available)

have worsened from 2012 -2017, likely owing to the ongoing opiate epidemic.[2]

Bauer and colleagues demonstrated that RDT, in conjunction with ASP, resulted in shorter lengths of stay by 6.2 days, and cost savings of $21,387 per episode of *S. aureus* bacteremia.[3] Parta et. al. found that implementation of RDT resulted in decreased vancomycin utilization for non-*Staphylococcus aureus* blood culture positivity, and shortened time to beta-lactam therapy for MSSA bacteremia.[4] While no studies have shown mortality benefit associated with RDT for *S. aureus* BSI alone, most have been underpowered to detect a difference.

Gram-negative Bacteremia

Several studies have investigated the utility of RDT in Gram-negative BSI. Bookstaver and others reported decreased empiric antipseudomonal beta-lactam and carabapenem duration (4.0 days to 2.5 days) when combined with an antimicrobial stewardship bundle.[5]

The Role of Antimicrobial Stewardship Programs

A consistent finding across most studies evaluating RDT implementation is the crucial role that ASP plays in clinical outcomes. Without active ASP involvement, most studies involving RDT fail to show any benefit related to antimicrobial utilization and patient outcomes. A randomized trial conducted by Banerjee and colleagues investigated the effect of multiplex PCR on treatment of BSI. While mPCR alone improved time to escalation of therapy with or without ASP, only the combination of mPCR and ASP resulted in shorter times to de-escalation.[6] Timbrook performed a systematic review and metanalysis of 31 studies encompassing 5290 patients which revealed a cumulative mortality odds ratio of 0.66 (0.54 – 0.88, 95% CI) in hospitals with ASP. Hospitals without dedicated ASP yielded a cumulative mortality odds ratio of 0.72 (0.46 – 1.12, 95% CI) when using RDT.[7]

All currently available RDT for BSI should be considered "add-on" testing, and do not replace conventional microbiology methods. Some platforms provide information regarding genotypic resistance, but cannot determine phenotypic expression. Even Accelerate Pheno, which provides limited phenotypic susceptibility testing does not provide results for narrow spectrum agents, or oral antibiotics. Therefore, laboratories implementing RDT for BSI are likely to incur additional costs which must be recuperated elsewhere. Pliakos and colleagues investigated the cost-effectiveness of RDT, and suggest that RDT is most cost-effective when implemented in conjunction with ASP, and in fact, may be cost-ineffective if implemented in the absence of ASP.[8]

Implementation in Community Hospitals

Several factors should be accounted for when considering implementation of RDT. First, the volume of the clinical syndrome affected should be sufficient to justify testing. For example, hospitals with infrequent cases of bacteremia are unlikely to benefit from BSI RDT modalities. Second, BSI RDT may be coupled with existing

platforms in the laboratory. BioFire, Cepheid, and GenMark all offer other RDT, and a lab may be able to perform multiple tests for different syndromes without additional need to purchase a new platform. Third, resources are required to provide education to interpreting clinicians who will act upon RDT. Finally, optimal outcomes are obtained when results are provided in real-time from a robust ASP. Interested readers are directed to a thoughtful review of RDT implementation published by Messacar.[9] Hospitals considering addition of RDT are encouraged to reach out to their DASON pharmacy liaison for assistance in optimization.

Key Points

- **Rapid diagnostic technology has improved speed with which microbiology results can be delivered to the clinician**
- **As a result, patients can experience quicker time to optimal therapy**
- **When coupled with ASP, RDT improved patient mortality. Effects are greatest when results are provided in real-time.**
- **Smaller clinical labs may benefit from introspective review to focus on specific needs related to volume and/or relevance rather than implementing wide, syndromic panel testing**

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